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Respiratory Virus Infections in Stem Cell Transplant Patients: The European Experience

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ABSTRACT

The frequency of and survival from community-acquired respiratory virus (CRV) infections among patients undergoing allogeneic or autologous stem cell transplantation (SCT) were evaluated in a prospective study conducted at 37 medical centers affiliated with the European Group for Blood and Marrow Transplantation. Of the 40 CRV infections diagnosed in 1863 patients (739, allogeneic SCT; 1124, autologous SCT), 20 were attributed to respiratory syncytial virus (RSV), 4 to parainfluenza viruses, and 16 to influenza virus A. The overall survival rate among SCT recipients with CRV infections was 76%; 8 patients, all recipients of allogeneic transplants, died after diagnosis of CRV infection, but only 5 of these deaths (3, RSV; 2, influenza A virus) were attributable to the infection. The overall rate of death directly attributable to RSV and influenza A virus infections in allogeneic SCT recipients was 1.1%. In an 18-month extension, an additional 53 patients with CRV were identified. Results for the combined data were similar to those from the first phase of the study.

KEY WORDS

Respiratory virus infection • Stem cell transplantation • Ribavirin

INTRODUCTION

Between October 1, 1997, and September 30, 1998, the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) conducted a prospective study of community-acquired respiratory virus (CRV) infections in all patients undergoing allogeneic or autologous stem cell transplantation (SCT) in the EBMT's 37 member institutions. The goal of the study was to determine the frequency of, risk factors for, and outcome of CRV infections in SCT recipients [1].

STUDY DESIGN

This study was a 1-year prospective study. All patients who underwent allogeneic or autologous SCT at EBMT institutions during the study period were enrolled. Each center used its own methods for diagnosing CRV infections, but all agreed to complete the same case report form.

Because a small number of respiratory infections occurred during the year of the original study (phase I), a second phase of the study was undertaken (phase II). During phase II, additional cases were collected prospectively for 18 months, beginning in October 1998, using the same procedures employed in phase I.

PHASE I RESULTS

Incidence of CRV Infection

During phase I, 819 patients underwent allogeneic SCT and 1154 patients underwent autologous SCT at the 37 EBMT centers. CRV infections developed in only 40 of these 1863 patients: 35 allogeneic and 5 autologous SCT recipients.

Pediatric transplantation centers reported the highest frequencies of CRV infection for both patient populations. Although the incidence of infection may actually have been higher at these centers than at other centers, the greater ease of diagnosis in pediatric patients, who have higher viral loads [2], as well as the centers' greater experience in looking for these infections might have contributed to the higher reported frequencies at these centers.

Of the 40 CRV infections diagnosed during phase I, 2 were present before the start of the conditioning period, 9 were diagnosed between 5 days prior to SCT and day 28 after SCT, and 29 occurred after engraftment (at day 29 or later). Of the 9 patients whose CRV infections were diagnosed before day 28, 7 underwent allogeneic SCT and 2 underwent autologous SCT. For those whose infections were diagnosed at day 29 or later, 26 of 29 were in the allogeneic SCT group.

Table 1. *Survival of SCT Recipients with CRV Infections at 37 EBMT Centers, 1997 to 1998*

	All Patients, Survived/Infected	Allogeneic SCT, Survived/Infected	Autologous SCT, Survived/Infected
Overall	31/40 (78%)	26/35 (74%)	5/5 (100%)
Time of diagnosis			
Before conditioning	2/2	2/2	NA
Days –5 to 28	7/9	5/7	2/2
≥Day 29	22/29	19/26	3/3
Virus			
RSV	15/20	13/18	2/2
Influenza A	12/16	10/14	2/2
Parainfluenza	4/4	3/3	1/1

Of the 40 CRV infections, 20 were attributed to respiratory syncytial virus (RSV), 4 to parainfluenza viruses, and 16 to influenza A virus. Of the 20 RSV infections, 14 (70%) were lower respiratory tract infections (LRTIs), whereas only 7 (44%) of 16 infections attributed to influenza virus A infections were LRTIs and only 1 (25%) of the 4 parainfluenza virus infections was an LRTI.

Survival Among Patients With CRV Infection

Overall, 78% of SCT recipients with CRV infections survived (Table 1). No differences in survival were seen among patients who acquired CRV infections prior to or following engraftment or before or after day 28 following SCT. Approximately 75% of patients survived CRV infection no matter when it occurred.

Survival rates for patients with RSV infections (80%) and those with influenza A virus infections (75%) were similar to the overall survival rate, whereas all patients with parainfluenza virus infections survived (Table 1).

We also examined the proximate cause of death among patients with a diagnosis of RSV or influenza A virus infection at the time of death. This analysis was performed in an attempt to arrive at a more precise definition of the outcome of CRV infection in this population. When CRV infection mortality was strictly defined as mortality due to respiratory failure caused by a specific virus, mortality among patients with CRV infection declined. Of the 20 patients with RSV infection, 5 died during the course of the study, but only 3 deaths were attributable to the RSV infection; 1 patient died of graft-versus-host disease and 1 patient died of aspergillosis. A similar analysis was applied to patients with influenza A virus infections. Of 16 patients with influenza A virus infection, 4 died, but only 2 died of influenza-related respiratory failure.

The respiratory virus–associated mortality rate among the allogeneic SCT recipients was 1.1%, which, although low, is still significant. No patients who underwent autologous SCT died of respiratory infections.

PHASE II RESULTS

During phase II of the study, 53 additional cases of CRV infection were identified, of which 31 were upper respiratory tract infections (URTIs) and 25 were LRTIs. As in phase I, the majority of CRV infections were caused by RSV (26 cases) or influenza A virus (23 cases), with parainfluenza virus accounting for 3 cases and rhinovirus for 1 case.

MORTALITY IN PHASE I AND PHASE II

The overall mortality rate for the combined phase I and phase II cases of CRV infection was approximately 25% (Table 2). The mortality rate for RSV infection was 30% overall but approached 35% in the allogeneic SCT population. Respiratory infection–associated mortality was 15% overall and approached 20% for RSV infections among allogeneic SCT recipients. For influenza A virus infections, the overall mortality rate was 23%, which is within the range reported in other studies [3,4], and the respiratory infection–associated mortality rate was 15%. Fatal influenza A virus respiratory infection occurred in 2 autologous SCT recipients.

RISK FACTORS FOR LRTI

Three factors were identified that placed patients at increased risk of LRTI: lymphocytopenia, neutropenia, and relationship to donor. However, multivariate analysis showed

Table 2. *Mortality Attributable to CRV Infection Among SCT Recipients with CRV Infections at EBMT Centers: Combined Results of Phases I and II*

	Infections, n	Deaths, n (%)	Deaths Due to Respiratory Virus, n (%)
Total	93	23 (25)	14 (15)
RSV (total)	46	14 (30)	8 (17)
Allogeneic SCT	42	14 (33)	8 (19)
Autologous SCT	4	0	0
Influenza A (total)	39	9 (23)	6 (15)
Allogeneic SCT	30	7 (23)	4 (13)
Autologous SCT	9	2 (22)	2 (22)
Parainfluenza virus	7	0	0
Rhinovirus	1	0	0

that only lymphocytopenia was a significant risk factor for LRTI among all patients with CRV infections (P = .008; odds ratio, 2.52; 95% confidence interval [CI], 1.26-5.06). Lymphocytopenia was also found to be a significant risk factor for LRTI among those with RSV infection (P = .01; odds ratio, 3.04; 95% CI, 1.26-7.35) but not among those with influenza virus infection (P = .11; odds ratio, 2.84; 95% CI, 0.73-11.01), probably owing to the low number of patients.

TREATMENT OF RSV INFECTION IN SCT RECIPIENTS

The most widely used treatment for RSV infection in immunocompromised patients is combination therapy with ribavirin and intravenous immunoglobulin (IVIG) [5-7], but ribavirin [8,9] may also be used alone.

Of the 33 patients with RSV URTI, 16 were untreated. None of these untreated patients died, whereas 1 of the 6 patients treated with ribavirin and IVIG died, and 2 of the 12 patients treated with ribavirin alone died. The impact of treatment on survival depends on the severity of the infection, which was not categorized among these patients. It is possible that only patients with severe illness were treated.

Treatment had a modest effect on all-cause mortality rates among SCT recipients with RSV LRTI. Of 54 such patients, 4 (40%) of the 10 patients who received no treatment survived; 5 (45%) of the 11 patients who received ribavirin plus IVIG survived; and 14 (50%) of the 28 patients treated with ribavirin alone survived. A controlled clinical trial would be necessary to determine the true effect of any treatment or of a particular treatment, given the 40% survival rate among untreated patients.

When the analysis was repeated excluding patients with RSV LRTI who died of another cause, intervention with either ribavirin or ribavirin plus IVIG had a slightly greater effect on survival than in the previous analysis.

Although intravenous ribavirin is not widely used in the United States, it has shown some promise, with or without aerosolized ribavirin, in a small uncontrolled European study of bone marrow transplantation recipients with proven CRV infection [10]. We therefore compared the outcomes for intravenous ribavirin versus inhaled ribavirin in SCT recipients with RSV LRTI. In these patients, ribavirin was similarly effective when administered by either route and with or without IVIG. Again, because 40% of patients in the untreated group survived, a controlled trial would be required to determine the comparative efficacy of these alternative treatments.

We also analyzed the effect of treatment with ribavirin on LRTI caused by parainfluenza virus. Six of 9 patients who received both intravenous and inhaled ribavirin and 8 of 15 patients who received only inhaled ribavirin survived; both groups also received IVIG.

CONCLUSIONS

In a prospective study enrolling 1863 patients undergoing SCT at 37 EBMT centers, CRV infections were diagnosed in approximately 2% of patients overall. The mortality rate associated with respiratory virus infection was approximately 1.1% among recipients of allogeneic SCT; no recipients of autologous SCT died of this cause. RSV and influenza A virus were responsible for most CRV infections in the allogeneic SCT group; RSV infections were responsible for higher respiratory virus–associated mortality rates than were influenza A virus infections. An 18-month extension of the prospective study that enrolled an additional 53 patients confirmed the study's essential findings and showed lymphocytopenia to be an independent risk factor for development of LRTI.

REFERENCES

1. Ljungman P, Ward KN, Crooks BNA, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2001;28:479-484.
2. Englund JA, Piedra PA, Jewell A, Patel K, Baxter BB, Whimbey E. Rapid diagnosis of respiratory syncytial virus infections in immunocompromised adults. *J Clin Microbiol*. 1996;34:1649-1653.
3. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. *Am J Med*. 1997;102(3A):2-9.
4. Ljungman P. Respiratory virus infections in bone marrow transplant recipients: the European perspective. *Am J Med*. 1997; 102(3A):44-47.
5. DeVincenzo JP, Leombruno D, Soiffer RJ, Siber GR. Immunotherapy of respiratory syncytial virus pneumonia following bone marrow transplantation. *Bone Marrow Transplant*. 1996;17:1051-1056.
6. Whimbey E, Goodrich J, Bodey G. Pneumonia in cancer patients. *Cancer Treat Res*. 1995;79:185-210.
7. Ghosh S, Champlin RE, Englund J, et al. Respiratory syncytial virus upper respiratory tract illnesses in adult blood and marrow transplant recipients: combination therapy with aerosolized ribavirin and intravenous immunoglobulin. *Bone Marrow Transplant*. 2000;25:751-755.
8. McColl MD, Corser RB, Bremner J, Chopra R. Respiratory syncytial virus infection in adult BMT recipients: effective therapy with short duration nebulised ribavirin. *Bone Marrow Transplant*. 1998;21:423-425.
9. Adams RH, Christenson JC, Petersen FB, Beatty PG. Pre-emptive use of aerosolized ribavirin in the treatment of asymptomatic pediatric marrow transplant patients testing positive for RSV. *Bone Marrow Transplant*. 1999;24:661-664.
10. Sparrelid E, Ljungman P, Ekelof-Andstrom E, et al. Ribavirin therapy in bone marrow transplant recipients with viral respiratory tract infections. *Bone Marrow Transplant*. 1997;19:905-908.